PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below 9-20-05

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/036958	04.11.2004	04.11.2003

International Patent Classification (IPC) or both national classification and IPC
A61K39/395, A61K38/20, A61P35/02

Applicant
CHIRON CORPORATION

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later. 9-20-05 9-4-05

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/036958

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-95 (IA)

because:

☒ the said international application, or the said claims Nos. 1-95 (regarding industrial applicability) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-95
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-95
Industrial applicability (IA)	Yes:	Claims	-
	No:	Claims	

2. Citations and explanations

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

PCT/US2004/036958

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-95 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following document/s/:

D1: WO 02/28480
D2: WO 02/28904
D3: WO 01/83755
D4: WO02/088186 (EP1391464)

2. For the assessment of the present claims 1-95 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

3. Independent claims 1 and 46 are directed to methods of treating cancer by administering in combination an antagonist anti-CD40 antibody and interleukin-2 (IL-2). All claims are further limited by two antibodies CHIR-5.9 and CHIR-12.12, the light or heavy chains of said antibodies, antibodies which bind the same epitopes or domain as CHIR-5.9 and CHIR-12.12 or which compete with the binding of the said

two antibodies. As the antibodies CHIR-5.9 and CHIR-12.12 are new (Article 33(2) PCT) and as the prior art does not disclose antibodies which bind the same domain or epitopes the methods of claims 1 and 46 using said antibodies are considered to be new (Article 33(2) PCT).

4. D1 discloses on page 4, lines 8-14 that anti-CD40 antibodies without any significant agonist activity can be used to treat several types of cancer relating to malignant B cells (which express CD40). D1 discloses also that the human anti-CD40 antibody 15B8 can be used. On page 30, line 15 D1 discloses that the antagonist anti-CD40 antibodies can be given in combination with IL-2.
The antibody 15B8 used in D1 is disclosed by its sequence in the co-pending application PCT/us01/30857, published as WO 02/28904(D2) , which shares the priority of D1. D2 discloses also that antagonist anti-CD40 antibodies like antibody 15B8 can be used to inhibit the growth of tumour cells (page 10, line 18). The only difference between of the present independent claims and the disclosure of D1 lies in the fact that the antibody of D1 does not bind to the same epitome or domain as the antibodies CHIR-5.9 and CHIR-12.12 but is only one example of known human antibodies against CD40, which do not have an agonist activity. Other human antibodies against CD40 are disclosed in:

D3, which discloses human anti-CD40 antibodies, which are a antagonists (page 9, lines 20-25). D3 discloses also the use of the anti-CD40 antibodies in the treatment of cancer (page 30, lines 1-7)

D4 discloses also several human anti-CD40 antibodies, which have an antagonist effect (example 14) .

The difference between the disclosure D1 and of the present independent claims lies in the use of different human anti-CD40 antibodies without significant agonist activities. The technical problem to be solved can be formulated as the provision of alternative anti-CD40 antibodies without significant agonist activities in the combined tumour treatment with IL-2. As the prior art D1 (D2), D3 and D4 disclose already antibodies having said properties and as the methods for producing human antibodies are well-known in the art, the provision of alternative antibodies cannot be

regarded as involving an inventive step (Article 33(3) PCT). As the features of the dependent claims do not involve any surprising effect, they do not confer an inventive step on the method either. Therefore the subject-matter of claims 1-95 does not involve an inventive step (Article 33(3) PCT).

Further Remarks

5. It should be noted that claims 6 and 47 are not supported by the description (Article 6 PCT), because the present description states clearly in example 4 on page 142 that the antibody CHIR-12.12 and IL-2 show additive anti-tumour activity.

6. Claims 24-26 and 28; 76-78 and 80 are not supported by the description (Article 6 PCT). The present application does not provide any substantive evidence that the two components of the claimed combination therapy can be given at different time points, including at an indefinitely long interval, and still have an additive effect on tumour growth.